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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,850	12/14/2001	Patrick M. Hughes	D-3004	7435

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EXAMINER	
SPIVACK, PHYLLIS G	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,850	HUGHES ET AL.	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *7 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,9 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' Amendment filed December 8, 2003 and response to the request for an election of species is acknowledged. Applicants have elected the species recited in claim 8, all quinoxaline compounds. Further, claims 17-23 are canceled. Claims 1-16 are presented.

Accordingly, claims 7 and 10 are withdrawn from consideration by the Examiner, 37 CFR 1.142(b), as directed to non-elected inventions. The subject matter presently under consideration are those pharmaceutical conjugates of claims 1-6, 8, 9 and 11-16, wherein the therapeutic component is a quinoxaline compound of instant claim 8.

Two Information Disclosure Statements filed December 14, 2001 and May 5, 2003, respectively, are acknowledged. The references have been reviewed to the extent each is presented in the English language.

Applicants are requested to send a list of co-pending or related applications when responding to this Office Action.

Claims 1-6, 8, 9 and 11-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The term "general" in the description of formula A has no probative value. Clarification is required.

Claims 1-6, 8, 9 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to

pharmaceutical conjugates comprising a quinoxaline compound of instant claim 8, an efficacy enhancing component of formula A that is, for example, memantine, wherein any of the R terms may be a C_1-C_{10} hydrocarbon. Further, claim 14 requires the pharmaceutical conjugate to have an aqueous solubility and a partition coefficient and/or an affinity for melanin that is greater relative to a compound comprising the same therapeutic component that is not joined to an efficacy enhancing component. The specification provides support for various pharmaceutical conjugates none of which comprise a quinoxaline compound of instant claim 8, an R term that is a C_1-C_{10} hydrocarbon nor data to support an aqueous solubility and a partition coefficient and/or an affinity for melanin that is greater relative to a compound comprising the same therapeutic component that is not joined to an efficacy enhancing component.

Attention is directed to In re Wands, 8 USPQ2d 1400 where the court set forth factors to consider when assessing whether or not a disclosure would require undue experimentation. These factors are:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation in view of further discussion below.

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The claimed invention relates to pharmaceutical conjugates comprising a quinoxaline compound of instant claim 8 and an efficacy enhancing component of formula A that is, for example, memantine. The recitation "hydrocarbon" encompasses any aliphatic or cyclic compound exclusively consisting of carbon and hydrogen.

The relative skill of those in the art is generally that of a Ph.D. or M.D. with expertise in the field of ophthalmology.

Each particular therapeutic component has its own specific characteristics and physical/chemical properties. The broad recitation "a pharmaceutical conjugate comprising a therapeutic component and an efficacy enhancing component" is inclusive of a plethora of diverse compounds.

It is clear the art to which the present invention relates is highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficacy.

The breadth of the claims

The claims are very broad and inclusive of any therapeutic component in any dosage form.

The amount of direction or guidance provided and the presence or absence of working examples

The working examples are limited to conjugates of bromonidine, insulin-like growth factor-1, ketoconazole, ciloxan and ganciclovir, all of which are ophthalmic drops. Preparation of the elected species is not disclosed.

The quantity of experimentation necessary

Applicants have failed to provide guidance as to which particular dosage forms of a conjugate of a quinoxaline compound of instant claim 8 and an efficacy enhancing component of formula A that is, for example, memantine, are contemplated, particularly in view of the requirement of the pharmaceutical conjugate to have an aqueous solubility and a partition coefficient and/or an affinity for melanin that is greater relative to a compound comprising the same therapeutic component that is not joined to an efficacy enhancing component. The skilled artisan in formulation chemistry would expect the combination of a particular therapeutic component and efficacy enhancing component in a conjugate formulation to be very specific absent a clear understanding of the structural and biochemical basis for each agent. The instant specification sets forth no such understanding nor any criteria for extrapolating beyond the combinations set forth in the Examples. Even for the combinations set forth, no direction is provided to prepare specifically a quinoxaline conjugate. One skilled in the ophthalmology art is provided no clear guidance as to the preparation of the elected species in a specific dosage form from among the many combinations of agents which are therapeutic and efficacy enhancing components. Since each prospective embodiment, as well as future

embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to prepare the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

Claim 8 is rejected under 35 U.S.C. 112, both first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make the invention, and for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

Applicants fail to particularly point out the definition of "derivatives" of the recited quinoxaline compounds. The metes and bounds of "derivatives" cannot be precisely determined. Numerous compounds that lack enablement and an adequate teaching as to how to prepare them are encompassed in the claim. Undue experimentation would be required to embrace the scope of the claims. Applicants should recite those derivatives contemplated.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 8, 9, 11-13, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over both Desantis, L., US 2001/0047012, and Collins et al., WO 01/92288.

Desantis teaches combination therapy for treating glaucoma comprising administering a glutamate antagonist and an intraocular pressure-lowering compound.

Brimonidine, 5-bromo-N-(4,5-dihydro-1H-imidazole-2-yl)-6-quinoxalinamine, a compound of instant claim 8, is a preferred intraocular pressure-lowering compound and memantine is a well established glutamate antagonist. See page 2, paragraphs [0018] and [0023]. Application to the eye encompasses topical administration. Collins teaches various pharmaceutical conjugates comprising a bioactive agent that is covalently bound directly or indirectly to a linker. Efficacy enhancing components of formula A are disclosed on page 92. Therefore, in view of the combined teachings of Desantis and Collins, one skilled in the art of formulation chemistry who seeks a pharmaceutical conjugate comprising a therapeutic component and an efficacy enhancing component of instant formula A would have been motivated to prepare a formulation comprising two known therapeutically effective ophthalmic agents in a formulation that is a conjugate to treat ocular pathologies. Such would have been obvious in the absence of evidence to the contrary because 1-aminoadamantane analogues such as memantine are established in the prior art as useful agents for conjugation with poorly soluble drugs. Such conjugates provide chemical stability and are known to dissociate under physiological conditions. Desantis establishes a therapeutic advantage of combining known ophthalmic drugs such as memantine and brimonidine. Collins teaches pharmaceutical conjugates with a low molecular weight linker to which a bioactive agent may be covalently bound. A conjugate in the form of a salt would reasonably be expected with modification of the pH.

No claim is allowed.

Any inquiry concerning this communication should be directed to Phyllis G. Spivack at telephone number 571-272-0585.

Phyllis Spivack

Phyllis G. Spivack
Primary Examiner
Art Unit 1614

April 3, 2004

PHYLLIS SPIVACK
PRIMARY EXAMINER